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# Thrombophilia and hormonal therapy in transgender persons: A literature review and case series

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**ABSTRACT**

***Background:*** Venous thromboembolism (VTE) is a rare side effect of hormonal therapy in transgender persons. Prothrombotic genetic variants can increase this risk. For this reason, previous VTE and/or genetic thrombophilia may be considered by some as contraindications to hormonal treatment.

***Aim:*** To formulate directions for clinical practice about the indications for thrombophilia screening and when to consider combination therapy of therapeutic anticoagulation and hormonal treatment as a safe alternative to withholding hormonal treatment.

***Methods:*** We conducted a literature search and describe a case series. All adult patients with gender dysphoria and a known prothrombotic genetic variant or history of VTE were invited by letter to participate in this study.

***Results:*** In our center, thrombophilia screening before start of hormonal treatment was restricted to those with a personal or family history of VTE. Sixteen individuals with a history of VTE and/or an underlying prothrombogenic condition were described. The time of follow up varied from 4 months to 20 years. Seven trans women had a positive thrombophilia screening (2 Factor V Leiden (FVL), 1 FVL + anticardiolipin antibodies, 1 FVL + high Factor VIII coagulant activity, 1 protein C deficiency, 1 prothrombin mutation, 1 positive lupus anticoagulant). Three trans women experienced an unprovoked VTE after start of hormonal therapy of which one lead to a positive thrombophilia screening. One VTE event in a trans woman was assumed to be provoked by surgery. Five trans men were identified with a prothrombogenic mutation (3 FVL, 1 protein C deficiency, 1 prothrombin mutation). One trans man, with a negative thrombophilia screen, experienced multiple provoked VTE events before start of hormonal therapy.

***Conclusion:*** Based on our literature review and case series we offer guidance when confronted with patients with previous VTE and/or genetic thrombophilia requesting hormonal interventions.

**KEYWORDS**
Anticoagulation; hormonal therapy; thrombophilia; thrombosis; transgender; case series; guidance

## Introduction

For trans women, or those requesting feminization, hormone therapy consists of estrogens, often with the addition of antiandrogens in the time period before or in the absence of orchiectomy. These antiandrogens include spironolactone, cyproterone acetate (which also has progesterone-like effects) and gonadotropin-releasing hormone agonists. 5α-Reductase inhibitors do not reduce testosterone levels and have adverse effects. Trans men, or those requesting virilization, can receive testosterone therapy, sometimes with the addition of progestins if menstrual bleeding occurs in the time period before or in the absence of hystero-oophorectomy (Hembree et al., 2017).

The side effects of this hormone therapy are limited, but remain an ongoing topic of research. Most commonly reported, venous thromboembolism (VTE) is a side effect that can cause important morbidity and mortality. Pulmonary embolism accounts for 8–13 per 1000 deaths in cis women and 2–7 per 1000 deaths in cis men among the age group 15–55 years (Barco et al., 2020). Many patient-related factors like age (Anderson et al., 1991), smoking (Pomp et al., 2008), obesity (Stein et al., 2005), surgery (White et al., 2003), major

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trauma (Geerts et al., 1994) or immobilization (Kierkegaard et al., 1987) contribute to this risk. Also prothrombotic genetic variants can severely increase this risk of hormone therapy. Heterozygous carriers of the Factor V Leiden (FVL) mutation have a 4- to 5-fold (Vandenbroucke et al., 1994) and homozygous carriers a 11-fold (Simone et al., 2013) increased risk for VTE. Heterozygous carriers of the Prothrombin G20210A mutation, Protein S and Protein C deficiency, Antithrombin deficiency have respectively a 3- to 4-fold (Margaglione et al., 1998), 5-fold (Pintao et al., 2013), 7-fold (Koster et al., 1995), 16-fold (Kumar et al., 2014) increased VTE risk. Elevated plasma factor VIII coagulant activity (VIII:C) is an independent marker of increased VTE risk with an odds ratio of 4.8 (Koster et al., 1995). For this reason previous VTE events and/or genetic thrombophilia are considered contraindications (cf. Table 1). If absolute contraindications exist, withholding hormonal treatment can lead to intense distress. So far, there are very few patient data available. We describe a single-center case series of transgender persons with a history of VTE and/or a known prothrombotic mutation treated at treated the Department of Endocrinology and Center for Sexology and Gender, Ghent University Hospital, Belgium. We review information that is essential to understand the rationale behind the used treatments.

## VTE risk of feminizing hormonal therapy

Type and dose of estrogen influence the association with VTE. Before the year 2000 approximately, ethinyl estradiol (EE), the most common estrogen in combined oral contraceptives (COC), was often used in trans women. We noted that sometimes the doses used in trans women were higher than doses used in COC in cis women (50–100 µg vs 10–40 µg per day). EE was associated with VTE. A retrospective study described 45 VTE cases in 816 trans women treated with 100 µg EE in combination with 100 mg cyproterone acetate between 1975 and 1994 (van Kesteren et al., 1997). This was in contrast to 17β-estradiol, the most potent naturally synthetized estrogen in the human body, that was associated with a much lower or even no increased

**Table 1.** Contraindications of feminizing and virilizing hormonal treatment.

| | Absolute contraindication | Relative contraindication |
|---|---|---|
| Feminizing treatment | • end stage chronic liver disease (Coleman et al., 2012)<br>• estrogen sensitive neoplasm (Coleman et al., 2012; Hembree et al., 2017)[a] or family history (Michel et al., 2001)<br>• unstable coronary artery disease (Hembree et al., 2017)[a]<br>• previous thromboembolic disease (Hembree et al., 2017; Michel et al., 2001)[b] related to an underlying hypercoagulable condition (Coleman et al., 2012) | • active smoking (Michel et al., 2001)<br>• cerebrovascular (Michel et al., 2001)[c] (Hembree et al., 2017)[a] or ischemic heart disease (Coleman et al., 2012)[d]<br>• marked hypertriglyceridemia (Hembree et al., 2017)[a] or hypercholesterolemia (Coleman et al., 2012)[d]<br>• obesity (Coleman et al., 2012; Michel et al., 2001)[d]<br>• severe hypertension (Michel et al., 2001)[c] (Coleman et al., 2012)[e]<br>• severe liver dysfunction(Michel et al., 2001)[c] (Coleman et al., 2012)[d]<br>• uncontrolled diabetes (Coleman et al., 2012)[f]<br>• cholelithiasis (Coleman et al., 2012)[d](Hembree et al., 2017)[a]<br>• untreated macroprolactinoma (Coleman et al., 2012; Michel et al., 2001)[c] (Hembree et al., 2017)[a] |
| Virilizing treatment | • estrogen sensitive neoplasm (Coleman et al., 2012)[g] (Hembree et al., 2017)[a]<br>• unstable coronary artery disease (Coleman et al., 2012; Hembree et al., 2017)[a]<br>• erythrocytosis (hematocrit > 48% (Bhasin et al., 2018), > 55% (Coleman et al., 2012))<br>• (intention for) pregnancy (Coleman et al., 2012) | • cerebrovascular (Hembree et al., 2017)[a] or ischemic heart disease (Coleman et al., 2012)[f]<br>• marked hypertriglyceridemia or hypercholesterolemia (Coleman et al., 2012; Michel et al., 2001)[e]<br>• obesity (Coleman et al., 2012; Michel et al., 2001)[d]<br>• severe hypertension (Coleman et al., 2012)[f] (Hembree et al., 2017)[a]<br>• severe liver dysfunction (Coleman et al., 2012)[e] (Hembree et al., 2017)[a]<br>• uncontrolled diabetes (Coleman et al., 2012; Michel et al., 2001)[f]<br>• erythrocytosis (hematocrit > 48%) (Bhasin et al., 2018)[h]<br>• obstructive sleep apnea syndrome (Coleman et al., 2012)[d]<br>• thrombophilia (Bhasin et al., 2018)[h] |

[a]Noted as 'moderate risk' of adverse outcomes (Hembree et al., 2017).
[b]Noted as 'very high risk of adverse outcomes'(Hembree et al., 2017).
[c]Noted as 'absolute contra-indications' (Michel et al., 2001).
[d]Noted as 'likely increased risk'(Coleman et al., 2012).
[e]Noted as 'possible increased risk' (Coleman et al., 2012).
[f]Noted as 'possible increased risk with additional risk factors'(Coleman et al., 2012).
[g]Noted as 'Because the aromatization of testosterone to estrogen may increase risk in patients with a history of breast or other estrogen dependent cancers, consultation with an oncologist may be indicated prior to hormone use.' (Coleman et al., 2012).
[h]Guidelines in cis gender population (Bhasin et al., 2018).

VTE prevalence rate between 0 and 5.5% (Asscheman et al., 2011; Goldstein et al., 2019; Khan et al., 2019; Shatzel et al., 2017). It is commercially available under the form of estradiol valerate (e.g. Progynova®), that is completely converted into the natural substances 17β-estradiol and valeric acid (Dusterberg & Nishino, 1982). The study of Toorians et al. was the first to investigate the effects of hormonal therapy in trans women on a number of hemostatic variables. Oral ethinyl estradiol (EE) induces a larger increase in activated protein C (APC) resistance, compared to both oral or transdermal 17β-estradiol in trans women (Toorians et al., 2003). This APC resistance is known as a major risk factor of VTE (Rosendaal, 1999). This observation led to a change in type of estrogen used in clinical care and nowadays estradiol valerate is recommended (Hembree et al., 2017). Interestingly, in the research of Toorians et al., the mean APC resistance in trans women on oral estradiol valerate or transdermal estradiol did not differ from that in trans men (or persons assigned female at birth) before start of hormonal therapy (Toorians et al., 2003). This finding is supported by a recent study that compared the coagulation profiles of trans women on estradiol therapy to cis men and cis women and found a procoagulant shift compared to cis men, but no significant changes compared to cis women (Lim et al., 2020).

Route of administration influences estrogen's association with VTE. There was a shift toward prescribing transdermal estrogens in older trans women, as VTE risk increased with age (Naess et al., 2007) and data in postmenopausal cis women showed that oral 17β-estradiol induced a significant more increase in APC resistance or thrombin generation compared to transdermal 17β-estradiol (Hoibraaten et al., 2001; Oger et al., 2003; Post et al., 2003; Scarabin et al., 2011). This is reflected in a lower VTE risk in cis women on transdermal treatment (Bergendal et al., 2016) (Roach et al., 2013). In a meta-analysis Olie et al. calculated pooled risk ratios for VTE of 1.9 [95% confidence interval (CI) 1.3–2.3] and 1.0 (95% CI 0.9–1.1) among oral and transdermal estrogen users, respectively (Olie et al., 2010). It must be noted that all data compared nonequivalent doses of transdermal (lower dose) and oral (higher dose) estrogens. A recent study about the effect of oral and transdermal estradiol in combination with CPA on coagulation profiles in trans women, found an overall procoagulant shift but very small differences between oral and transdermal preparations, in favor of transdermal applications (Scheres et al., 2021). Another recent study found no differences in coagulation parameters between oral and transdermal estrogens in trans women (Lim et al., 2020). However a large observational study did show fewer cases of thromboembolism since the introduction of transdermal estradiol in the treatment of trans women over 40 years of age (van Kesteren et al., 1997). More recent data in trans women on oral estradiol valerate or transdermal formulations show lower VTE rates or even no increased risk of VTE compared to the cisgender female population (Asscheman et al., 2011; Goldstein et al., 2019; Khan et al., 2019; Shatzel et al., 2017). One study showed that all 11 thrombotic events in 214 trans women occurred in the presence of other risk factors such as smoking, recent surgery, dyslipidemia or hypertension (Wierckx et al., 2013).

As is the case in cis women, data in trans women suggest an additional VTE risk associated with the use of progestins like cyproterone acetate. Toorians et al. observed an increase in APC resistance after start of cyproterone acetate monotherapy in trans women from 1.4 ± 0.6 to 1.8 ± 0.9 (P-value 0.016) (Toorians et al., 2003). An alternative to cyproterone acetate as anti-androgen treatment is spironolactone or gonadotropin-releasing hormone agonists (GnRHa) (Hembree et al., 2017). Spironolactone is the most common used anti-androgenic drug in trans women in the United States and research investigating its safety profile, do not report on VTE (Lainscak et al., 2015). Next to a competitive inhibitor of the aldosterone receptor, spironolactone also inhibits the androgen receptor as well as the testicular steroidogenesis. In vitro data suggest a role of aldosterone in hemostasis (Ducros et al., 2008; Gromotowicz et al., 2011) and the association between VTE and drospirenone, a progestin with similar structure to spironolactone and similar anti-mineralocorticoid and antiandrogen effects, has been the subject of much debate (Lidegaard

et al., 2009; Seeger et al., 2007). Gonadotropin-releasing hormone agonists (GnRHa) are not associated with an increased risk of VTE in cis women (Somers et al., 2005). There is not much known about the risk of GnRHa in healthy cis men, but they are assumed safe. There are some data in oncological settings with cis male patients on androgen deprivation therapy (Ehdaie et al., 2012) for prostate cancer. Cyproterone acetate monotherapy increases the risk of VTE compared to orchiectomy or gonadotropin-releasing hormone agonists (Seaman et al., 2007). The overall high thrombosis rate found in this population must however be seen in the context of an active malignancy.

### *VTE risk of virilizing hormonal therapy*

VTE risk in trans men on testosterone therapy is low. Different observational series in trans men showed no incidence of VTE (De Cuypere et al., 2005; Ott et al., 2010; Schlatterer et al., 1998; Wierckx et al., 2012; 2013; 2014). One study reported a single event of venous thrombosis in 293 trans man in the postoperative period (van Kesteren et al., 1997). In all series testosterone was administered intramuscular and in some up to 30% of the participants were current smokers. Testosterone therapy can lead to erythrocytosis and secondary polycythemia. In case of myeloproliferative neoplasms, this erythrocytosis is associated with thrombosis, but the literature regarding this risk in the context of testosterone-induced erythrocytosis (in cis men) remains a matter of debate (Baillargeon et al., 2015; Jones et al., 2015). In most reports of VTE associated with testosterone use in cis men, erythrocytosis was not present or not reported (Freedman et al., 2015; Glueck et al., 2018; Kavoussi et al., 2019). Nevertheless, the Endocrine Society recommends that testosterone therapy should be withheld in cis men who develop hematocrit >54% until it has returned to the normal range and then resume therapy at a lower dose. They graded this recommendations as of low quality (Bhasin et al., 2018). A study showed that trans men on testosterone undecanoate, an oil vehicle-based formulation injected intramuscularly every 12 weeks results in more stable serum concentrations, exhibited lower erythrocytosis rates (Δ 0.8 hematocrit %), compared to trans men on testosterone esters, which are injected every 2 weeks. In this study of 192 trans men, 10 of 109 patients on testosterone undecanoate (9.2%) developed serum hematocrit levels ≥50.0% during a three year follow-up period, seven of 44 patients on testosterone esters (15.9%), and five of 39 patients on testosterone gel (12.8%) (Defreyne et al., 2018). On the other hand, a recent study of Madson et al. found a higher odds for hematocrit levels >0.50 L/L for long-acting undecanoate intramuscular injections (2.9 95% CI 1.7–5.0) than for short-acting esters (1.1 CI 0.7–1.6), both compared to transdermal applications during a 20 year follow-up period (Madsen et al., 2021). At the level of the coagulation cascade, testosterone therapy in both cis and trans men, as well as in cis women, does not induce procoagulant changes (Agledahl et al., 2009; Anderson et al., 1995; Bland et al., 2005; Buckler et al., 1998; Chang et al., 2018; Scheres et al., 2021; Toorians et al., 2003).

The purpose of the current paper is to give an overview of VTE-related problems in trans people from a large practice with 20 year clinical experience and to advise colleagues when confronted with questions on hormonal therapy and thrombosis.

## Materials and methods

We conducted a literature search through PubMed and Embase, using following search terms: transgender, transsexual, hormone or hormonal therapy, estrogens, oral contraception, hormone or hormonal therapy, testosterone, coagulation cascade, thrombophilia, thromboembolism, VTE, thrombosis. Additional papers were found through cascading the references of included articles. Both the population in background papers, as our own patients are described as trans women or trans men, based on terminology used in the papers and on self-identification, respectively.

All adult patients with gender dysphoria and a known prothrombotic genetic variant or history of VTE, were invited by letter in December 2019 to participate in this study. We received a 100% response rate. All are Caucasian. Data collection

from their medical files occurred from December 2020 until January 2021. The cohort was selected by the endocrinologist from the gender team (G.T.), who treated all transgender individuals (approximately 1700; 720 trans men and 970 trans women) at the Department of Endocrinology and Center for Sexology and Gender, Ghent University Hospital, Belgium over a 20 year time period, since the year 2000.

## Results

In our center, in accordance with the Endocrine Society Clinical Practice Guideline on endocrine treatment of gender-dysphoric/gender-incongruent persons, thrombophilia screening before start of hormonal treatment is restricted to those with a personal or family history of VTE (Hembree et al., 2017). This screening includes the Factor V Leiden (FVL) mutation, presence of the lupus anticoagulant and anticardiolipin antibodies, Factor II or Prothrombin mutation, Factor VIII coagulant activity and Protein C/S/antithrombin deficiency. In our cohort of approximately 1700 transgender individuals, who chose hormonal intervention, 16 individuals (6 trans men and 10 trans women) with a history of VTE and/or an underlying prothrombogenic condition were described. The time of follow up (at the moment of data collection) of these individuals varied from 4 months to 20 years.

### *Trans women or assigned male at birth (AMAB)*

Seven trans women had a positive thrombophilia screening (2 FVL, 1 FVL + anticardiolipin antibodies, 1 FVL + high Factor VIII coagulant activity, 1 protein C deficiency, 1 prothrombin mutation, 1 positive lupus anticoagulant). One trans women was screened because of a family history of VTE; her mother was homozygous carrier of the FVL mutation and had experienced a DVT. Another trans woman was screened in another hospital before start of hormonal therapy because of unspecified reasons (no family history of VTE) and she was started on therapeutic anticoagulation there at the start of hormonal therapy because of the finding of a FVL mutation in combination with the presence of anticardiolipin antibodies. Four of these trans women were screened because of a personal history of VTE before start of hormonal therapy, and 1 in response to an unprovoked pulmonary embolism (PE) 8 years after start of hormonal therapy. All were advised combination therapy of transdermal estrogens and anticoagulation. One trans woman decided to stop estrogens after one year and another trans woman chose CPA monotherapy until gender affirming surgery without estrogens. The trans woman who experienced an unprovoked PE while on transdermal estrogen and CPA, turned out to be carrier of the FVL. At the time, hormonal therapy was stopped during 6 months while she was anticoagulated. After this 6 months spironolactone monotherapy was restarted in combination with anticoagulation until orchidectomy. Afterwards transdermal estrogens were again introduced in combination with anticoagulation. Four trans women experienced a VTE 8 months to several years after start of hormonal therapy. Three of these VTE events were unprovoked and one was assumed to be provoked by surgery. Only one case (described above) lead to a positive thrombophilia screening. She was treated with transdermal estrogens, while the other 3 were treated with oral estrogens. Two trans women were advised lifelong anticoagulation in combination with transdermal estrogens. The other two were one trans woman who's PE was assumed to be provoked by her gender affirming surgery and thus unrelated to her estrogen use as she stopped her estrogens 2 weeks before surgery. In our opinion there was no need to continue therapeutic anticoagulation lifelong - after of course the necessary period to treat the PE. In the other trans woman, estrogens were stopped after a postoperative TIA while under CPA monotherapy at age of 33 and an unprovoked extensive deep vein thrombosis (DVT) when on estrogens at the age of 51. No trans women experienced a (new) VTE event under anticoagulation, even if 2 continued smoking and two were obese (BMI > 35 kg/m$^2$) (Table 2).

### *Trans men or assigned female at birth (AFAB)*

Four trans men with a family history of VTE, were identified with a prothrombogenic mutation

**Table 2.** Case series feminizing treatment.

| | | | | VTE events | | | Treatment | | |
|---|---|---|---|---|---|---|---|---|---|
| case | age[a] | thrombophilia screening[b] | family history | before start HT | (time period) after start HT | other risk factors | at the moment of the event | current therapy | FU |
| 1 | 32 | FVL | Mother FVL, DVT | – | – | BMI >35 kg/m$^2$ | td E2 100 µg/d + VKA | | 3 y |
| 2 | 41 | FVL | Negative | – | PE (8 y) | – | td E2 75 µg + CPA 25 mg/d | td E2 3 mg + spironolactone 200 mg (4 m)[c] + rivaroxaban 20 mg/d | 8 y |
| 3 | 20 | FVL, anticardiolipin antibodies | Negative[d] | – | – | – | td E2 25 µg + rivaroxaban 20 mg/d | | 4 y |
| 4 | 52 | FVL, high FVIII coagulant activity | Father PE | 4x DVT | – | Smoking (stop at start HT) | – | td E2 1.5 mg/d + VKA, stop E2 after 1 y[e] | 4 y |
| 5 | 36 | Protein C deficiency | Unknown | V. Cava thrombosis | – | Smoking | – | CPA 50-100 mg (1 y)[c] + td E2 50 µg/d + VKA later switch rivaroxaban 20 mg | 14 y |
| 6 | 46 | Prothrombin G20210A mutation | Negative | ocular thrombosis | – | – | – | CPA (2 y)[c] no estrogens[e] | 15 y |
| 7 | 33 | Positive lupus anticoagulans | Negative | DVT + PE | – | Smoking | – | td E2 1.5 mg + spironolactone 100 mg[c] + edoxaban 60 mg/d | 4 m |
| | | | | DVT | | Smoking | -[f] | | |
| 8 | 33 | Negative | | | | | | edoxaban 60 mg/d | 33 y |
| | | | Unknown | – | DVT (18y) | BMI > 35 kg/m$^2$ | Premarin[g] 0.625 mg/d | | |
| | | | | | DVT (33 y) | BMI > 35 kg/m$^2$ | – | | |
| 9 | 21 | Negative | Niece DVT + LE[h] | – | PE (8m) | – | oral E2 2 × 2 mg + CPA 12.5 mg | td E2 1.5 mg + CPA 12.5 mg + rivaroxaban 20 mg/d | 10 m |
| 10 | 42 | Negative | Negative | – | PE (2 y)[h] | Surgery | oral E2 2 × 2 mg + CPA 25 mg /d[i] | oral E2 2 mg/d | 10 y |

HT: hormonal treatment.
FU: follow-up since start hormonal treatment.
FVL: Factor V Leiden (heterozogous).
BMI: body mass index.
y: years.
td: transdermal.
E2: estradiol.
VKA: Vitamine K antagonists.
PE: pulmonary embolism.
CPA: cyproterone acetaat.
m: months.
DVT: deep vein thrombosis.
iCVA: ischemic cerebrovascular event.
ASA: acetylsalicyl acid.
[a]Age at start of gender affirming hormonal therapy.
[b]This screening consists of: Factor V Leiden, lupus anticoagulans and anticardiolipin antibodies, Factor II or Prothrombin mutation, Factor VIII coagulant activity, Proteine C/S/antithrombin deficiency.
[c]Until orchidectomy.
[d]Unknown reason for screening, no family history, the screening was performed in another hospital.
[e]Patient's preference to stop estrogens.
[f]Second DVT after she stopped her anticoagulation on her own initiative, she was advised lifelong anticoagulation.
[g]Conjugated equine estrogen, isolated from pregnant horse urine, historically the first exogenous estrogen product (FDA approved in 1942) for treatment of hot flashes associated with menopause.
[h]Her niece had this DVT and LE in a period of immobilization while the was on thrombosis prophylaxis.
[i]Preventive stop of estrogens two weeks before surgery.

(2 FVL, 1 protein C deficiency, 1 prothrombin mutation). They had the following family history: a mother with a known FVL mutation who suffered from a DVT and a PE (case 1-Table 3), a mother with a known FVL mutation who had a DVT (case 2), a mother who experienced a DVT in the context of COC use, a maternal aunt with a known protein C and S deficiency and a maternal grandmother with a DVT and maternal grandfather with a PE (case 4), a mother with a known Prothrombin G20210A mutation who had two PE (case 5). One trans man was screened

**Table 3.** Case series virilizing treatment.

| | | | | VTE events | | | | treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|
| case | age[a] | Thrombophilia screening[b] | Family history | Before start HT | (Time period) after HT | Hematocrit | Other risk factors | At the moment of the event | Current therapy | FU |
| 1 | 17 | FVL | Mother FVL DVT + PE | – | – | | – | IM TU 1 g/14w | | 6 y |
| 2 | 17 | FVL | Mother FVL, DVT | – | – | | – | IM TU 1 g/13w | | 6 y |
| 3 | 24 | FVL | Unknown | – | – | | Smoking BMI > 35 kg/m$^2$ | IM TEs 250 mg /2w | | 9 y |
| 4 | 16 | Protein C deficiency | Extensive[c] | – | – | | – | IM TU 1 g / 12w | | 3 y |
| 5 | 18 | Prothrombin G20210A (PT) mutation | Mother PT mutation, 2xPE | – | – | | Smoking | IM TEs 125 mg / 2w | | 5 y |
| 6 | 62 | Negative | Negative | DVT<br>DVT + PE | <br>PE (4 y) | <br>46.6 % | Surgery immobilization<br>– | –<br>LMWH prev.dose<br>td T 46 mg/d + VKA[d] | td T 46 mg /d + VKA | 5 y |

HT: hormonal treatment.
FU: follow-up since start hormonal treatment.
FVL: Factor V Leiden (heterozogous).
DVT: deep vein thrombosis.
PE: pulmonary embolism.
IM: intramuscular.
TU: Testosterone Undecanoaat.
w: weeks.
y: years.
BMI: body mass index.
TEs: Testosterone Esters (in 1 ml: decanoaat 100 mg, isocaproaat 60 mg, fenylpropionaat 60 mg, propionaat 30 mg).
LMWH prev. dose: low molecular weight heparines in preventive dose.
td: transdermal.
T: Testosterone.
PT: Prothrombin G20210A mutation.
VKA: Vitamine K antagonists.
TIA: transient ischemic attack.
ASA: acetylsalicyl acid.
[a]Age at start of gender affirming hormonal therapy.
[b]This screening consists of: Factor V Leiden, lupus anticoagulans and anticardiolipin antibodies, Factor II or Prothrombin mutation, Factor VIII coagulant activity, Proteine C/S/antithrombin deficiency.
[c]His mother had a DVT in the context of COC use, maternal aunt was known with a Protein C and S deficiency, maternal grandmother had a DVT, maternal grandfather had a PE.
[d]4 years after start hormonal treatment, cave no INR controls during preceding 3 months because of the COVID-19 pandemia. Sintrom was chosen, after bleeding complications in the past under rivaroxaban.

for unknown reasons and carried the FVL mutation (case 3). None of them had a personal history of VTE. All were treated with intramuscular testosterone. No one developed a VTE while on this treatment during a follow-up period ranging from 3 to 9 years, while 2 were active smokers of which one was obese (BMI > 35 kg/m$^2$). One trans man experienced multiple provoked (after surgery and after immobilization despite prophylaxis with low molecular weight heparines) VTE before start of hormonal therapy. His thrombophilia screen was negative, but because of the multiple VTE events (one despite thrombosis prophylaxis), lifelong anticoagulation was indicated. When starting hormonal therapy, transdermal testosterone was chosen. Four years after start of this combination therapy he experienced a pulmonary embolism. This event could possibly be related to a period of inadequate anticoagulation, as no INR controls took place during the three months preceding this VTE event (in the context of the Covid-19 pandemia). After this event, the testosterone treatment was interrupted for 6 months.

## Discussion

Based on different guidelines (Bhasin et al., 2018; Coleman et al., 2012; Hembree et al., 2017; Michel et al., 2001) listing absolute and relative contraindications for hormonal treatment, withholding or stopping treatment seems sometimes indicated. Unfortunately, these guidelines lack any suggestions for a solution when hormonal treatment is essential. The impact on a transgender person's quality of life and future of avoiding treatment cannot be underestimated. Besides the negative psychological impact, withholding

hormonal treatment, especially after gonadectomy, has negative effects on bone health. This is learned from studying bone mineral density in trans men after gonadectomy when not on testosterone therapy (Goh & Ratnam, 1997) and from postmenopausal bone loss in cis women (Wells et al., 2002).

### *Trans women or assigned male at birth (AMAB)*

In our series, in trans women with a positive thrombophilia screen (and family history of VTE, as this was the indication for screening) regardless of the presence of a personal history of VTE therapeutic anticoagulation was initiated if estrogens were started. One trans woman without personal or family history of VTE, was started on therapeutic anticoagulation (in another hospital) maybe because of the presence of two prothrombogenic factors: FVL and anticardiolipin antibodies. The rationale behind this is the known supra-additive VTE risk of estrogens in the form of COC or oral hormonal replacement therapy (HRT) in cis women with thrombophilia like the FVL, Prothrombin mutation or high Factor VIII coagulant activity (Bergendal et al., 2014; Bloemenkamp et al., 1999; Douketis et al., 2011; Emmerich et al., 2001; Roach et al., 2013; Vandenbroucke et al., 1994). All trans women with a known history of unprovoked or recurrent VTE at intake, regardless of their thrombophilia screen, were treated with anticoagulation from the start of hormonal treatment. In case of a VTE event after start of hormonal therapy, therapeutic anticoagulation was immediately added, while hormonal therapy was interrupted for 6 months. During exploration, there were more events in trans women compared to trans men (4 vs 1). Most events were several years after start of hormonal therapy. This VTE incidence with longer duration of hormonal therapy is in concordance with other data in trans women (Getahun et al., 2018), but in contrast to data in cis women were most events were in the first few months after starting (Lidegaard et al., 2009; Roach et al., 2013). Three of the four trans women experiencing a VTE after start of hormonal therapy, were on oral estrogens, of whom one was on Premarin®, a historically used conjugated equine estrogen, known to be associated with an increased VTE risk in postmenopausal cis women (Cushman et al., 2004). Combination therapy of estrogens and therapeutic anticoagulation, is supported by the research of Martinell et al., that showed that hormonal contraception in cis women was not associated with an increased risk of recurrent VTE when receiving therapeutic anticoagulation (Martinelli et al., 2016). The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis also recommends to consider combination therapy of anticoagulation and COC in case of strong gynecological indication or patient's personal preference (Baglin et al., 2012). It is prudent to use transdermal estrogens, as data in both cis and trans women showed that they are less thrombogenic compared to oral estrogens (Bergendal et al., 2016; Olie et al., 2010; Roach et al., 2013; van Kesteren et al., 1997), and a meta-analysis found no increased VTE risk in cis women with prothrombotic mutations (FVL, Prothrombin mutation) on transdermal HRT (Canonico et al., 2008). If anti-androgen treatment is desired, spironolactone or a gonadotropin-releasing hormone agonist (GnRHa) is preferred over CPA, as data in both cis and trans women suggested an additional VTE risk with the use of progestins like CPA in association with estrogens (Asscheman et al., 1989; Goldstein et al., 2019; van Kesteren et al., 1997; Wierckx et al., 2013), as well as in monotherapy (Seaman et al., 2007; Toorians et al., 2003).

### *Trans men or assigned female at birth (AFAB)*

In our series, in trans men with a positive thrombophilia screen but without personal history of VTE, testosterone was started without therapeutic anticoagulation. The rationale behind this, is in contrast with 2 clinical case control series in cis men that hypothesize that testosterone therapy can interact with underlying thrombophilia through hypofibrinolysis promoting VTE. They found that, compared to VTE controls not on testosterone therapy, the VTE cases on testosterone were more likely to have FVL heterogeneity, high Factor VIII coagulant activity or the lupus anticoagulant. After a first VTE event and

continuing testosterone, they had a second or even third VTE despite adequate anticoagulation, this in the absence of an elevated hemoglobin (Freedman et al., 2015; Glueck et al., 2018). However, the overall incidence of VTE in trans men on testosterone therapy is low (De Cuypere et al., 2005; Ott et al., 2010; Schlatterer et al., 1998; Wierckx et al., 2012; 2013; 2014) and testosterone does not cause a clear prothrombogenic shift in the coagulation cascade (Scheres et al., 2021; Toorians et al., 2003). In our case series, only 1 VTE event occurred in trans men after start of hormonal therapy, out of a total of approximately 720 trans men treated. His hematocrit was normal at the time of the incident. This trans man was already advised lifelong anticoagulation independently of the testosterone use because of his personal history of recurrent VTE before start of testosterone therapy. The VTE event may have occurred in a period of inadequate anticoagulation. Some advocate to prefer testosterone undecanoate formulations or testosterone gel to testosterone esters, as they induce lower rates of erythrocytosis (Defreyne et al., 2018), although a causal link between testosterone induced secondary erythrocytosis and VTE remains a matter of debate (Baillargeon et al., 2015; Jones et al., 2015). Guidelines advise differently. The Endocrine Society Clinical Practice Guideline on treatment of gender-dysphoric/gender-incongruent persons (Hembree et al., 2017) state that a hematocrit > 50% is associated with a very high risk of adverse outcomes. In the Endocrine Society Clinical Practice Guideline on testosterone therapy in men with hypogonadism (Bhasin et al., 2018), there is a recommendation against starting testosterone when hematocrit is > 48% (50% for men living at high altitude) and to stop testosterone therapy if hematocrit is > 54%. The World Professional Association for Transgender Health (WPATH) (Coleman et al., 2012) states that a hematocrit of 55% or higher is an absolute contraindication to testosterone therapy. In case of polycythemia vera, erythrocytosis is associated with a high thrombosis rate. In this context, the British Society for Hematology advises to maintain the hematocrit under 45% through phlebotomy (McMullin et al., 2005), as this target had a significantly lower rate of major thrombosis than a hematocrit target of 45 to 50% (Marchioli et al., 2013). Another advantage of testosterone gel, next to the reported lower chance of erythrocytosis, is the short duration of action, implying the possibility to be stopped immediately in case of a VTE event. When using progestins in thrombophilic trans men in case of uterine bleeding, caution is warranted, as it is known that high dose progestins in cis women and especially when carrying the FVL mutation, augments the VTE risk (Bergendal et al., 2014).

### *Risks of therapeutic anticoagulation*

While therapeutic anticoagulation can prevent the occurrence of thrombosis, it is not without risk and can cause major bleeding if not well monitored. For each individual patient, the risk benefit balance must be taken into account in the shared decision making on hormonal therapy.

### *Thrombophilia screening*

As all individuals with a history of unprovoked VTE, regardless the result of their thrombophilia screen, were treated with anticoagulation from the start of hormonal treatment, one can critically notice that a thrombophilia screening in these patients is not really necessary and that this screening (when available) can be reserved for trans women without a personal history but with a strong positive family history (≥ 2 first degree relatives) of VTE. We agree with Conners et al. that the decision to screen for inherited thrombophilia in these trans women, must be similar to the approach in cis women before starting estrogens and should not be performed routinely as it has low utility and is not cost-effective (Connors & Middeldorp, 2019). We must note that testing in cis women is controversial. Conners et al. stated in their review (concerning the cisgender population) that this testing may guide informed decision making about starting estrogens in cis women with first-degree family members with a history of VTE and a known inherited thrombophilia. If family members have not been tested, the suspicion for an inherited thrombophilia is high when they were affected at young

age (before 40–50 years), when the VTE events were recurrent, unprovoked or in unusual sites (central nervous system or splanchnic veins) (Connors, 2017). Also, a negative or absent (when not available) thrombophilia screening in combination with a strong family history of VTE does not indicate a low risk of VTE.

### *Prevalence of thrombophilic defects*

We note that according to the overall prevalence of thrombophilic defects in the general Caucasian population of 7% (Lee et al., 1996; Miletich et al., 1987; Rees et al., 1995; Rosendaal et al., 1998; Tait et al., 1995), we can assume that many more transgender individuals in our population carry (unidentified) thrombophilic defects while on hormonal therapy (without anticoagulation) and without experiencing VTE events. This is also illustrated in a study of Ott et all. who found an APC resistance in 7.2% of their transgender population on hormonal treatment, without the incidence of VTE (Ott et al., 2010). A meta-analysis in cis women showed that heterozygous carriers of the FVL or the prothrombin gene mutation without a family history of VTE, have only a modest additional risk of VTE when they use COC (van Vlijmen et al., 2016). Based on this, we advise therapeutic anticoagulation in trans women with a known thrombophilia and a positive family history of VTE, as the only reason for thrombophilia screening in these cis women was their positive family history.

### *Limitations*

There are limitations to our study, as the design is a case series, that is retrospective and subject to selection bias. Although there may have been trans persons lost to follow-up, the number of patients is substantial. As no intramuscular formulations are available in our country and sublingual use of oral estrogens is only rarely mentioned, these have not been studied. In our literature search, we could not find data concerning the VTE risk of sublingual or intramuscular estrogens. We speculate that, for sublingual administration because of no first pass metabolism, this risk is low. On the contrary, as intramuscular application may induce supraphysiological peak levels, the risk could be elevated. However no clinical data sets are currently available to confirm these assumptions. In the future, it would be interesting to investigate the incidence of VTE, (genetic) thrombophilia and other vascular events in transgender persons on hormonal therapy with our without anticoagulation in a larger European prospective cohort study. Also, the cohort was Caucasian, therefore the risk may not be generalizable to other cohorts.

## Conclusion and directions for clinical practice

Based on our literature review and case series we suggest the following:

1. In trans women with a family history of VTE in ≥ 2 first degree relatives or in one first degree relative with a known thrombophilia, we recommend a thrombophilia screening, when available.
2. In trans men with an asymptomatic known thrombophilia, we do not recommend therapeutic anticoagulation when testosterone therapy is started. We do advise avoiding high dose progestins (in case of uterine bleeding).
3. In trans women with an asymptomatic known thrombophilia and family history of VTE, we discuss therapeutic anticoagulation when estrogen therapy is started. We advise transdermal over oral estrogens, and spironolactone or gonadotropin-releasing hormone agonists over CPA.
4. In trans men and trans women with a personal history of unprovoked or recurrent VTE, we recommend hormonal therapy in combination with therapeutic anticoagulation. In case of trans women, we advise transdermal over oral estrogens, and spironolactone or gonadotropin-releasing hormone agonists over CPA.
5. To reduce the risk of VTE development, for all, we recommend smoking cessation, weight loss if overweight or obese.

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The authors have no conflict of interest to declare.

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